the second synthesis procedure, thereby determining whether a difference between the first and second synthesis procedure affects the efficiency of the second synthesis procedure.

I. Status of the Application

Claims 1-8, 10-15 and 37-39 are presently pending in the application. Claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 112, first paragraph for various reasons of record. Claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being unpatentable over Lam et al. US Patent No. 5,650,489 (102(e) date of at least 6/19/91). Claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lam et al. US Patent No. 5,650,489 (102(e) date of at least 6/19/91) in view of Fodor et al. Science 251: 767 (1991) and Applicants' disclosure of the prior art teachings. Claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lam et al. US Patent No. 5,650,489 (102(e) date of at least 6/19/91) in view of Holmes US Patent No. 5,679,773 and Applicants' disclosure of the prior art teachings.

Applicants have amended the claims under consideration to more clearly define and distinctly characterize Applicants' novel invention. Support for the amendments to claims 1 and 10 is found at page 14, line 28 to page 15, line 13 and throughout the specification. The amendments add no new matter.

Applicants respectfully request entry and consideration of the foregoing amendments which are intended to place this case in condition for allowance.

II. The Rejections of the Claims Under 35 U.S.C. § 112, First Paragraph

At page 2, paragraph 3 claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 112, first paragraph. At page 3, paragraph 4, claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 112, first paragraph. As to the first rejection, the Examiner states that the claims encompass a genus that is indefinitely large because the specification only discloses peptide and nucleotide libraries. Regarding the second rejection, the Examiner states that the specification enables nucleotides, peptides and peptide nucleic acids but does not reasonably provide enablement of an array of diverse polymers.

In response, Applicants have amended claims 1 and 10 to specify "synthesizing a preselected array of diverse ***biological*** polymers connected to cleavable linkers on a solid support". The specification provides at page 14 line 28 to page 15, lines 13 that biological polymers are composed of biological monomers that include natural and synthetic amino acids, nucleotides, nucleosides, phosphoramidites, and carbohydrates. In addition, page 2 lines 12-14 of the specification incorporates by reference USSN 07/980,523 (US Patent No. 5,677,195) which provides many example of biological polymers that are attached to a substrate. See col. 5 line 41 to col. 6 line 48 of the '195 patent. Applicants respectfully submit that claims as amended to include the term "biological polymers" fully meet the written description and enablement requirements of 35 U.S.C. In view of the above, Applicants respectfully request withdrawal of the rejections of claims 1-8, 10-15 and 37-39 under 35 U.S.C. § 112, first paragraph.

III. Claims 1-8, 10-15 and 37-39 Are Patentable over Lam et al.

At page 5 paragraph 7, claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being unpatentable over Lam et al. US Patent No. 5,640,489 (102(e) date of at least 6/19/91) (Lam et al.).

Applicants respectfully traverse the Examiner's rejection. The methods of Lam et al. fail to teach or suggest the claimed step of synthesizing a ***preselected array*** of diverse biological polymers connected to cleavable linkers on a solid support. The specification of the instant application defines a "polymer array" and a "preselected array of polymers" at page 15, lines 25-29:

> A "polymer array" is a spatially defined pattern of polymers on a solid support. A "preselected array of polymers" is a spatially defined pattern of polymers on a solid support which is designed before being constructed (*i.e.*, the arrangement of polymers on solid substrate during synthesis is deliberate, and not random).

In stark contrast, Lam et al. (as recognized by the Examiner at page 6 lines 1-2 of the office action) teaches synthesis of a ***random library*** of biopolymers on beads, wherein ***each bead contains a single biopolymer*** and not a spatially defined pattern of polymers on a solid support. The Examiner further recognizes at page 10 that Lam et al did not actually prepare and analyze the arrays of polymeric molecules on supports and hence conduct the methods set forth in the instant claims. As evidence of this, Lam et al. itself in discussing Fodor and others states that "none of the other conventional peptide synthesis methods provide for the synthesis of a library of peptides bound to a solid support that is truly random". See Lam at col. 4. Lam et al. further states at col. 4 that "none of the prior peptide synthesis methods provides for the synthesis of a library of greater than 10^5 peptides in which a single peptide species [is] attached to a single

solid phase support." In further distinguishing Fodor, Lam states respectively at col. 3 lines 48-52 and col. 4 lines 5-20:

> The method of Fodor, et al., utilizes a "light-directed spatially addressable parallel chemical synthesis" technique. This technique is also limited by the relative lack of development of photochemical peptide synthesis methods.
>
> Although useful, as a practical matter the chemical techniques of Geysen, Fodor, Houghton, Berg and Furka and co-workers allow the synthesis and testing of only hundreds to a few thousand peptides at a time. These techniques are quite limited in light of the millions of possible peptide sequences, one or more of which might correspond to the binding sites between the entities of interest. With 20 known common amino acids, in any sequence of five amino acids, there are 20^5, or about $3.2X10^6$, possible amino acid combinations. None of the procedures enable the synthesis of this many peptides at one time. Further multiplicity results by varying peptide chain length. Similarly, conventional peptide synthesis, such as that described in Stewart and Young (1984, *Solid Phase Synthesis*, Second Edition, Pierce Chemical Co., Rockford, Ill.) does not provide a method for synthesis of thousands to millions of peptides at a time.

Applicants respectfully submit that Lam et al. itself teaches against synthesizing a preselected array of diverse biological polymers on a solid support as claimed by applicants. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. Such is plainly the case with the disclosures in Lam et al. Lam et al. very clearly discourages against using the methods of Fodor identified therein for the reasons stated in col. 4 and focuses clearly on the use of a single biopolymer on a single bead to produce random libraries. No teaching can be found in Lam et al., including the mere identification of spatially addressable arrays of Fodor et al. at col. 3 lines 47-52, which counters the clear teaching away from using a preselected array of diverse biological polymers on a solid support as claimed by applicants in the amended claims now

presented. Since Lam et al. fails to teach or suggest applicants' claimed subject matter, applicants respectfully request that the Examiner withdraw his rejection based on 35 U.S.C. § 102(e).

The Examiner is further respectfully requested to withdraw his rejection of the claimed subject matter as being obvious in view of Lam et al. for the reasons stated above. Lam et al. expressly discourages the modification proposed by the Examiner, i.e. use of a preselected array of diverse biological polymers on a solid substrate.

Moreover, the present invention is not drawn to a single polymer attached to a single bead, and is not amenable to the complete coupling methods taught by Lam et al. to achieve its random library. For example, the present invention provides methods for monitoring and optimizing the efficiency of polymer array synthesis, which includes the length distribution of synthesized species and the presence, nature and extent of truncated species (see page 18, lines 2-13 of the specification). The method of Lam et al. is not concerned with examining the length of synthesized species after the complete, overall synthesis of the random biopolymers because Lam et al. teaches examining and assuring the length of biopolymers during each synthetic coupling step of an overall synthesis. Specifically, Lam et al. teaches "complete coupling," as exemplified at col. 8, lines 44-46, in which the coupling reaction is driven to completion irrespective of the differences in the coupling rates of individual amino acids. Lam et al. therefore provides no motivation, and in fact, teaches away from any need or desire to measure the length of polymers or the presence of truncated polymers by measuring the size of polymers cleaved from a biosynthetic synthesis support after overall synthesis is complete. The complete

coupling methods taught by Lam et al. are not applicable to synthesizing a preselected array of diverse biological polymers on a solid substrate.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 1-8, 10-15 and 37-39 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Lam et al.

IV. Claims 1-8, 10-15 and 37-39 Are Patentable over Lam et al. In View of Fodor et al.

At page 8, paragraph 8 claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lam et al. US Patent No. 5,640,489 (102(e) date of at least 6/19/91) (Lam et al.) in view of Fodor et al. Science 251: 767 (1991) (Fodor et al.) and Applicants' disclosure of the prior art teachings.

The Examiner states it would have been obvious to one of skill in the art to monitor synthesis of polymer arrays as taught by Fodor et al. using a method as taught by Lam et al., because Lam et al. teach the desirability of monitoring polymer array synthesis. Applicants respectfully traverse the Examiner's rejection based on the arguments provided above with respect to the anticipation and obviousness rejections based solely on Lam et al.

Lam et al. teaches away from using a preselected array of diverse biological polymers on a solid substrate as stated above. Lam et al. teaches synthesis of a single polymer on a single bead, and also teaches synthetic means of complete coupling at each step of an overall synthesis which are not compatible with the synthesis of polymer arrays according to the present invention.

The Examiner has stated that limitations taught by Lam et al. with respect to polymer arrays are not in the analysis of the arrays of the present invention, rather they are in the size of the arrays and techniques for generating the arrays. Applicants respectfully point out that the claimed subject matter recites the synthesis and use of a preselected array of diverse biological polymers on a solid support. Nowhere does Lam et al. teach or suggest this limitation.

As the Examiner acknowledges, Fodor et al. teaches the synthesis of polymer arrays on substrates where each member of the polymer array occupies a different region of the substrate. More specifically, Fodor et al. teaches the synthesis of polymer arrays using photochemistry in a manner to define the products and their locations on the array. Fodor et al. does not teach or suggest removal of polymers from the array for analysis. Applicants submit that because Fodor et al. is not concerned with generating a random array and/or cleaving an array to analyze it, Fodor does not provide one of skill in the art any motivation to look to Lam et al. or to combine its teachings with those of Lam et al. Further, as stated above, Lam et al. very clearly discourages against using the methods of Fodor identified therein for the reasons stated in col. 4. Additionally, Lam et al. specifically teach away from using the methods set out in Fodor as shown in the quotations from Lam above. It is difficult to see how Lam and Fodor should be combined if Lam has expressly stated that Fodor is limited and is distinguished from his method.

In view of the above, Applicants respectfully submit that the claimed invention is nonobvious over Lam et al. in view of Fodor et al. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-8, 10-15 and 27-39 under 35 U.S.C. § 103(a) over Lam et al. in view of Fodor et al.

V. Claims 1-8, 10-15 and 37-39 Are Patentable Over Lam et al. In View of Holmes

At page 14, paragraph 10, claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lam et al. US Patent No. 5,640,489 (102(e) date of at least 6/19/91) in view of Holmes US Patent No. 5,679,773 and Applicants' disclosure of the prior art teachings. The Examiner emphasizes that the embodiment of Holmes discussed at col. 19 lines 33-58 discusses the cleavage of array members from a support and comparison with standards to provide a confirmation of synthesis fidelity. Applicants respectfully traverse the rejection as to the amended claims now presented. Lam et al. teaches against the use of a preselected array of diverse biological polymers on a solid support. Holmes, like Fodor, discusses the preparation of polymers in preselected areas of a solid support. Thus it is in the category of art that Lam et al. has distinguished themselves from and consequently does not provide the necessary motivation to combine the references in the manner suggested by the Examiner in view of the explicit teaching against provided by Lam et al.

Also, Applicants respectfully submit that while col. 19 lines 33-58 discusses assays for determination of synthesis fidelity, that embodiment describes assays for the analysis of a labeled polymer, rather than a preselected array of polymers. This is evident at col. 19, lines 49-52, which states:

> This method comprises first synthesizing a labeled polymer on a solid support. Subsequent cleavage of the labeled polymer from the support and comparison with known standards provides a confirmation of synthesis fidelity.

There is no suggestion to combine Holmes with Lam et al., but even if there was, the combination fails to cure the deficiencies of Lam et al. Accordingly, Applicants respectfully

request withdrawal of the rejection of claims 1-8, 10-15 and 37-39 under 35 U.S.C. § 103(a) over Lam et al. in view of Holmes.

VI. Conclusion

Applicants have shown that there is a wide range of polymers shown and described in the specification that are in the class of biological polymers. Additionally, Applicants have shown that Lam et al. fail to teach Applicants' invention especially in light of the teaching away from Fodor and Holmes. Having addressed all outstanding issues, applicants respectfully request entry and consideration of the foregoing amendments and reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

Dated: December 18, 2000

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